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(54) Osteogenic devices

(57) Disclosed are 1) osteogenic devices comprising a matrix containing osteogenic protein and methods of inducing endochondral bone growth in mammals using the devices; 2) amino acid sequence data, amino

acid composition, solubility properties, structural features, homologies and various other data characterizing osteogenic proteins, and 3) methods of producing osteogenic proteins using recombinant DNA technology.

FIG. 1A-1

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10      20      30      40      50      60      70
GGAGGTATAGGAGCTCTCTCGATTTAGCAAACAGGAGTCCGAAGATCTAAGGAGAGCTGGGGGTTTGACTCC
      SacI
85      95      105     115     125     135     145
GAGAGCTCGAGCAGTCCCAAGACCTGGTCTTGACTCAGGAGTTAGACTCCACTCAGAGGCTGACTGTCTCCAGG
      SacI      PflMI
160     170     180     190     200     210     220
GTCTACACCTCTAAGGGCGACACTGGGCTCAAGCAGACTGCCGTTTCTATATGGGATGAGCCTTCACAGGGCAG
      235     245     255     265     275     285     295
CCAGTTGGGATGGGTTGAGGTTGGCTGTAGACATCAGAAACCAAGTCAATGCGCTTCAACAGTAGAAAAATT
      310     320     330     340     350     360     370
CACCAGCCCCGAGAGCTAAGGTTGGGTGGACATTAGGTTGGTTGATCCAGGAGCTCAACAGTGTCTCTGAGCC
      385     395     405     415     425     435     445
CCAGCTCCTTCTGCCCAACCCACCATCTTCAGTGTGCTTCTCTCAAGGCCACAGCTGTAGTTGGCCAGGGGG
      PvuII      BallI
460     470     480     490     500     510     520
GCTTCATTATTTTGTCTGGGCGAGTAGGAGGAAGAGAATGATGCTCTCCATGGGTCTTCTTAGGAATGT
      NcoI
535     545     555     565     575     585     595
GGGAACCTTTTCCAGAAGTCTCTATGCTTTTAGTTTGTGTTGGGTCACTTGGCCTTCTCAACCACTTCTCGAC
      610     620     630     640     650     660     670
TCTCGGACAGGATGTGCACTGATGACCTTAGCTTTGGGATCTAATAGTCACTTTACAAAGCCTCTTTGAGAAG
      ApaLI      EspI
685     695     705     715     725     735     745
TGACATTGGAACCAAGGCTTGAGCAGACACAACAAAGATTGCAGGGAGGGCATTGCAGGTGGAGGAAACGGCAC
      BspMI-
760     770     780     790     800     810     820
ATGCAAGAGCCCTGCGTGGGAGTGAGCTGTGTTTGGTCAATCACTGTCTCAGAGCACACGGGGCCCTGTCAAGCA
      ApaI      EcoRI

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FIG. 1A-2

[illegible]

1810 1820 1830 1840 1850 1860 1870
 GTCTTGTGCTCAATCTCCAGTTAAGACTCCAGTATCAAGTGGCTCTCGTAGGGAAGGCTACTTGCTTAAGCA
 1885 1895 1905 1915 1925 1935 1945
 TATCTGGT.....(APPROX. 1000 BASES).....GGAGACGACGATGCTGATGCCATTATGA
 1960 1970 1980 1990 2000 2010 2020
 GTTATTAGCTCTCTGCGACCTGCCAACCCGAGGCGATGAGCGTTCTTTAAGGTGAACCTGCCATGTGTGCATCA

1A-3 BspH1- Dr

FIG. 1A-3

	7035	7045	7055	7065	7075	7085	7095	7105
CTCAGTCTGAGCTGAGCTGATGCTGCTCAGACCGAGCTCTCTCTGCTGCTGCTTCTGACGAGCAGACAGC								
A1111				BacI				M
M1								
	2118	2120	2130	2140	2150	2160	2170	2178
CATGATGATCTCATTTTGTAGATGACCGAAGCGCTCTCTCTCTCAATTTTATTTATCTTTTGTAGAAATTCGG								
co1								
	2185	2195	2205	2215	2225	2235	2245	2255
GTCTTGCTCTCTCACCAGAGCTGGTGCTAGCTGCTGATCATGCTGACCGAAGCTTCTCTCTCTCTTCCGATC								
						Tth1111		
	2260	2270	2280	2290	2300			2320
CAGCTCTAAGTACCTTGACATAGGCGACATAGAGCTGCTCTCTCTCTCTCTTTCTTGGGACGACATCGAGAG								
Ma11111					BalXI			
	2335	2345	2355	2365	2375	2385	2395	2405
CCACCACTTTTCTGCGCCCTCTGGGCTCTGCTCTCAGAGGACATGGTCTGAGCTTTACCTCTTGCTGAG								
		Apel						
		EcoO						
	2430	2420	2430	2440	2450	2460	2470	2470
TTCTCTGCTGGTGTCTTCTTTCAGCACTGGCTGGGATGCTGCTCTCTCTCTCTCTCTCTCTCTCTCTCTCT								
2485	2495	2505	2515	2525	2535	2545	2555	2565
CTCTCTCTCAGAGATGATGATCTGCTGGCTGAGCTGATGATGATGATGATGATGATGATGATGATGATGATGAT								
Ma1111				Qse111				
	2580	2570	2580	2590	2600	2610	2620	2620
TGACCTCTCATCTATCAAGCGGACCAACAGCATGATGATGATGATGATGATGATGATGATGATGATGATGATGAT								
	2635	2645	2655	2665	2675	2685	2695	2705
TCACTTGTTCGGGACGACCTGGCGAGCGGACAGATGATGATGATGATGATGATGATGATGATGATGATGATGAT								
(D111) Dp11								

FIG. 1A-4

[illegible]

FIG. 1A-5,

[illegible]

FIG. 1A-6

4585 4595 4605 4615 4625 4635 4645
 CTGCAGTCATTTCATTATGCCAGACAGGATGTTTCTTTATAGAAACGTGGAGGCCAGTTAGAACGACTCACCGCT
 pMI+
 PstI
 4660 4670 4680 4690 4700 4710 4720
 TCTCACCAGTGGCCATGTTTGGTGTGTGTTTCAGGTCCACTTCATCAACCCGGAAACGGTGCCCAAGCCCTGCT
 PflMI
 4735 4745 4755 4765 4775 4785 4795
 GTGCGCCACGCAGCTCAATGCCATCTCCGTCCTTACTTCGATGACAGCTCCAACGTCATCCTGAAGAAATACA
 4810 4820 4830 4840
 GAAACATGGTGGTCCGGGCTGTGGCTGCCACTAGCTCCTCCGA

FIG. 1B

CONSENSUS PROBE 20 30 40 50 60 70
 GATCCTAATGGGCTGTACGTGGACTTCCAGCGGACGTGGGCTGGGACGACTGGATCATCGCCCCGTCG
 ** ** * * * * *
 TGTAAGAAGCAGCAGCTGTATGTCAGCTTCCGAGACCTGGGCTGGCAGGACTGGATCATCGCGCTGAAG
 OP4 28 38 48 58 68 78 88
 80 90 100 110 120 130 140
 ACTTCGACGCCTACTACTGCTCCGGAGCCTGCCAGTTCCCTCTGCGGATCACTTCAACAGCACCAACCA
 ** * * * * *
 GCTACGCGCGCTACTACTGTGAGGGGAGTGTGCCTTCCCTCTGAACTCCTACATGAACGCCACCAACCA
 98 108 118 128 138 148 158
 150 160 170 180 190 200 210
 CGCCGTGGTGCAGACCCCTGGTGAACAACATGAACCCCGCAAGGTACCCAAGCCCTGCTGCGTGCCCAACC
 **** * * * * *
 CGCCATCGTGCAGACGCTGGTCCACTTCATCAACCCGGAAACGGTGCCCAAGCCCTGCTGTGCGCCACG
 168 178 188 198 208 218 228
 220 230 240 250 260 270 280
 GAGCTGTCCGCCATCAGCATGCTGTACCTGGACGAGAATTCCACCGTGGTGCTGAAGAACTACCAGGAGA
 **** * * * * *
 CAGCTCAATGCCATCTCCGTCCTTACTTCGATGACAGCTCCAACGTCATCCTGAAGAAATACAGAAACA
 238 248 258 268 278 288 298
 290 300 310
 TGACCGTGGTGGGCTGCGGCTGCCGCTAACTGCA
 ** * * * * *
 TGGTGGTCCGGGCTGTGGCTGCCACTAGCTCCT
 308 318 328



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EUROPEAN SEARCH REPORT

Application Number
EP 01 20 1546

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-The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14 May 2002	Examiner van de Kamp, M
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EPO FORM 1503 03/82 (P04/01)



European Patent
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Application Number

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-15 (all partially)



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EUROPEAN SEARCH REPORT

Application Number
EP 01 20 1546

DOCUMENTS CONSIDERED TO BE RELEVANT			
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-The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14 May 2002	Examiner van de Kamp, M
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 01 20 1546

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-15 (all partially)

Use of a composition consisting of a single species of osteogenic protein as active osteogenic ingredient, said protein comprising of an unpaired polypeptide chain or which protein does not comprise a pair of polypeptide chains and is capable of inducing endochondral bone formation when disposed within a matrix and implanted in a mammal, for the manufacture of a medicament for inducing endochondral bone formation, wherein the protein comprises the sequence VPKPCCAPT or LYCSF-to-ACGHC or HQRQA-to-ACGHC (according to claim 8a-c). Said osteogenic protein in unglycosylated form, a process for its production, and a polypeptide producible by said process. Said use, protein, process or polypeptide wherein the protein has an apparent molecular weight of 30 kD in the glycosylated native form (27 kD in deglycosylated form), or comprises two polypeptide chains with apparent molecular weights of 16 and 18 kD in glycosylated form (14 to 16 kD in glycosylated form). Processes for producing an osteogenic device comprising disposing said protein in a matrix, for implantation in a mammal.

2. Claims: 1-15 (all partially)

Use of a composition consisting of a single species of osteogenic protein as active osteogenic ingredient, said protein comprising of an unpaired polypeptide chain or which protein does not comprise a pair of polypeptide chains and is capable of inducing endochondral bone formation when disposed within a matrix and implanted in a mammal, for the manufacture of a medicament for inducing endochondral bone formation, wherein the protein comprises the sequence CKRHP-to-GCGCR (according to claim 8d). Said osteogenic protein in unglycosylated form, a process for its production, and a polypeptide producible by said process. Said use, protein, process or polypeptide wherein the protein has an apparent molecular weight of 30 kD in the glycosylated native form (27 kD in deglycosylated form), or comprises two polypeptide chains with apparent molecular weights of 16 and 18 kD in glycosylated form (14 to 16 kD in glycosylated form). Processes for producing an osteogenic device comprising disposing said protein in a matrix, for implantation in a mammal.

3. Claims: 1-15 (all partially)

Use of a composition consisting of a single species of osteogenic protein as active osteogenic ingredient, said protein comprising of an unpaired polypeptide chain or which



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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 01 20 1546

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

protein does not comprise a pair of polypeptide chains and is capable of inducing endochondral bone formation when disposed within a matrix and implanted in a mammal, for the manufacture of a medicament for inducing endochondral bone formation, wherein the protein comprises the sequence CRRHS-to-GCGCR (according to claim 8e). Said osteogenic protein in unglycosylated form, a process for its production, and a polypeptide producible by said process. Said use, protein, process or polypeptide wherein the protein has an apparent molecular weight of 30 kD in the glycosylated native form (27 kD in deglycosylated form), or comprises two polypeptide chains with apparent molecular weights of 16 and 18 kD in glycosylated form (14 to 16 kD in glycosylated form). Processes for producing an osteogenic device comprising disposing said protein in a matrix, for implantation in a mammal.

4. Claims: 1-15 (all partially)

Use of a composition consisting of a single species of osteogenic protein as active osteogenic ingredient, said protein comprising of an unpaired polypeptide chain or which protein does not comprise a pair of polypeptide chains and is capable of inducing endochondral bone formation when disposed within a matrix and implanted in a mammal, for the manufacture of a medicament for inducing endochondral bone formation, wherein the protein comprises the sequence CARRY-to-SCACR (according to claim 8f). Said osteogenic protein in unglycosylated form, a process for its production, and a polypeptide producible by said process. Said use, protein, process or polypeptide wherein the protein has an apparent molecular weight of 30 kD in the glycosylated native form (27 kD in deglycosylated form), or comprises two polypeptide chains with apparent molecular weights of 16 and 18 kD in glycosylated form (14 to 16 kD in glycosylated form). Processes for producing an osteogenic device comprising disposing said protein in a matrix, for implantation in a mammal.



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T	OZKAYNAK E ET AL.: "OP-1 cDNA encodes an osteogenic protein in the TGF-beta family" EMBO JOURNAL, vol. 9, no. 7, 1 July 1990 (1990-07-01), pages 2085-2093, XP000611252 ISSN: 0261-4189 * the whole document *		TECHNICAL FIELDS SEARCHED (Int.Cl.7)
-The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14 May 2002	Examiner van de Kamp, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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EPO FORM 1503 03.82 (P04C01)

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